--This application is a continuation-in-part of U.S. Application Serial No. 08/346,293, filed November 23, 1994, issued as U.S. Patent No. 5,487,994, which is a continuation-in-part of Serial No. 08/126,564, filed September 27, 1993, issued as U.S. Patent No. 5,436,150, July 25, 1995, which is a continuation-in-part of U.S. Application Serial No. 08/017,493, filed February 12, 1993, abandoned, which is a continuation-in-part of U.S. Application Serial No. 07/862,831, April 3, 1992, issued as U.S. Patent No. 5,356,802.--

IN THE CLAIMS:

Please amend the pending claims as follows:

25 ~~1.~~ 1 (Amended) A method of claim ~~9~~ wherein

said cell in which said nuclease is to be produced is to be cloned, and

said cell comprises said target nucleic acid and said target nucleic acid is required for cloning [non-natural and natural restriction endonucleases with co-expression of DNA ligase] of said cell,

said method further comprising the steps of:

[a)] c) [preparing a first plasmid containing a gene] providing a third polynucleotide encoding a DNA ligase; and

[b)] d) [transfecting cells with the first plasmid so] delivering said third polynucleotide to said cell before or concurrently with said step of delivering said preparation of said first polynucleotide into said cell, under conditions such that said DNA ligase is produced whereby said target nucleic acid is protected by said DNA ligase from inactivation by said nuclease produced in said cell;

[c) preparing a second compatible plasmid containing a gene encoding a hybrid restriction endonuclease;

d) transfecting said cells with said second plasmid;] and

e) cloning said [cells] cell producing said nuclease and said ligase.

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~~2.~~ (Amended) The method of claim ~~1~~, wherein said [cells are] cell is a prokaryotic [cells] cell.

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~~3.~~ (Amended) The method of claim ~~2~~, wherein said [cells are] cell is an *E. coli* [cells] cell.

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~~4.~~ The method of claim ~~1~~, wherein said [cells are] is a eukaryotic [cells] cell.

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~~5.~~ (Amended) The method of claim ~~4~~, wherein said [cells are] cell is a plant [cells] cell.

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~~6.~~ (Amended) The method of claim ~~4~~, wherein said [cells are] cell is a mammalian [cells] cell.

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~~7.~~ (Amended) The method of claim ~~1~~, wherein said [cells are] cell is a mutant or engineered [strains of cells] strain that [produce] produces an increased [levels] level of DNA ligase.

38. (Amended) The method of claim 25, wherein said [gene encoding a hybrid restriction endonuclease] nuclease is selected from the group consisting of ZF-QDR-F_N, ZF-Sp1C-F_N, ZF-QNR-F_N, ZF-QQR-F_N and ZFHD1-F_N.

39. (Amended) A method for [enzymatically inactivating] producing a nuclease in a cell wherein

said nuclease, when produced in a cell comprising a target [DNA] nucleic acid which comprises a target nucleotide sequence, specifically binds to said target nucleotide sequence and cleaves said target nucleic acid specifically bound to said nuclease,

said method comprising the steps of:

a) [preparing a plasmid, phage, virus or any other delivery vehicle such as a liposome containing a gene] providing a preparation of a first polynucleotide encoding [a] said nuclease, wherein said [nuclease] preparation does not comprise a second polynucleotide encoding an enzyme which protects said target nucleic acid from said nuclease by specifically [recognizes] binding to said target nucleotide sequence and enzymatically [inactivates] modifying said target [DNA] nucleic acid such that said target nucleic acid is not cleaved by said nuclease; and

b) delivering [the plasmid, phage, virus or any other delivery vehicle such as a liposome containing the gene] said preparation of said first polynucleotide encoding [a] said nuclease into [cells] said cell under conditions such that said first polynucleotide expresses said nuclease, thereby producing said nuclease [;

c) inducing said cells to produce said nuclease; and

d) enzymatically inactivating said target DNA].

2 ~~10.~~ (Amended) The method of claim 1 ~~9~~, wherein [the gene] said polynucleotide encoding [a] said nuclease is delivered into [cells] said cell by [way of] liposomes.

3 ~~11.~~ (Amended) The method of claim 1 ~~9~~, wherein said delivering step further comprises integrating [the gene] said first polynucleotide encoding [a] said nuclease into a chromosome of said [cells] cell.

4 ~~12.~~ (Amended) The method of claim 1 ~~9~~, wherein [the gene] said polynucleotide encoding [a] said nuclease further comprises control elements.

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5 ~~13.~~ (Amended) The method of claim 1 ~~9~~, wherein said [cells are] cell is a prokaryotic [cells] cell.

6 ~~14.~~ (Amended) The method of claim 5 ~~13~~, wherein said [cells are] cell is an *E. coli* [cells] cell.

7 ~~15.~~ (Amended) The method of claim 1 ~~9~~, wherein said [cells are] cell is a eukaryotic [cells] cell.

8 ~~16.~~ (Amended) The method of claim 7 ~~15~~, wherein said [cells are] cell is a plant [cells] cell.

9 ~~17.~~ (Amended) The method of claim 7 ~~15~~, wherein said [cells are] cell is a mammalian [cells] cell.

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~~19.~~ (Amended) The method of claim ~~9~~, wherein said nuclease is a non-naturally [occuring restriction] occurring enzyme.

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~~20.~~ (Amended) The method of claim ~~19~~, wherein said nuclease [is a hybrid restriction endonuclease] comprises a recognition domain which specifically binds to said target sequence and a separate catalytic domain which cleaves nucleotide sequences non-specifically and is obtained from a nuclease not comprising said recognition domain.

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~~21.~~ (Amended) The method of [claim 20] claim ~~29~~, wherein [said gene encoding] said nuclease is selected from the group consisting of ZF-QDR-F_N, ZF-Sp1C-F_N, ZF-QNR-F_N, ZF-QQR-F_N and ZFHD1-F_N.

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~~22.~~ (Amended) The method of [claim 9] claim ~~27~~, wherein said target [DNA] nucleic acid is [a DNA] exogenous to [DNA of] said [cells] cell.

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~~23.~~ (Amended) The method of claim ~~22~~, wherein said target [DNA] nucleic acid is [any] a self-replicating DNA, linear or circular.

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~~24.~~ (Amended) The method of claim ~~22~~, wherein said target [DNA] nucleic acid is [a DNA] a replication intermediate of an RNA tumor virus.

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~~25.~~ (Amended) The method of [claim 9] claim ~~27~~, wherein said target [DNA] nucleic acid is a DNA endogenous to [DNA of] said [cells] cell.

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~~26.~~ 21 (Amended) The method of claim ~~25~~ 20, wherein [the target DNA] said target nucleic acid is chromosomal DNA of said [cells] cell.

Please add the following new claims 27-32:

--~~27.~~ 16 A method of claim ~~9~~ 1 wherein said cell in which said nuclease is to be produced comprises said target nucleic acid and said target nucleic acid is to be specifically inactivated,

wherein further said nuclease produced in said cell specifically inactivates said target nucleic acid by specifically binding to said target nucleotide sequence and cleaving said target nucleic acid bound to said nuclease.

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~~28.~~ 13 A method according to claim ~~26~~ 12 wherein said catalytic domain is obtained from the *FokI* restriction endonuclease.

~~29.~~ 14 A method according to claim ~~26~~ 12 wherein said recognition domain comprises a zinc finger domain.

~~30.~~ 22 A method according to claim ~~9~~ 1 wherein said target nucleic acid is a DNA:RNA hybrid.

~~31.~~ 23 A method according to claim ~~9~~ 1 wherein said target nucleotide sequence comprises a sequence of more than 6 nucleotides.

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